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EXAMINER	
DUNSTON, JENNIFER ANN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,112	MORI ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,28,29,31-37,39,40,46-54 and 56-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,28,29,31-37,39,40,46-54 and 56-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 July 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 5/3/2010, in which claims 25-27, 30 and 55 were canceled, and claims 24, 28, 46, 56 and 65 were amended. Claims 24, 28, 29, 31-37, 39, 40, 46-54, 56-65 are pending and under consideration.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Claim Objections

Claim 65 is objected to because of the following informalities: the claim language is confusing due to the wording of the claim, specifically the phrase "chimeric protein of ecdysone receptors." The chimeric protein set forth in the claim is not a chimera composed of a plurality of ecdysone receptors. Rather, it is a chimeric protein containing a single ecdysone receptor fragment, which is the ligand binding domain of HecR. It would be remedial to amend the claim to delete "of ecdysone receptors" or to replace the phrase "of ecdysone receptors" with the phrase "of an ecdysone receptor" or "chimeric ecdysone receptor protein."

Response to Arguments - Claim Objections

Applicant's arguments filed 5/3/2010 have been fully considered but they are not persuasive. The response asserts that Applicants have amended the claim according to the Examiner's suggestion. However, the phrase "chimeric protein of ecdysone receptors" was not changed, as suggested in the prior action, to "a chimeric ecdysone receptor protein."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 28, 29, 31, 37, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Garger et al (US Patent Application Publication No. 2002/0061309 A1; see the entire reference). This is a new rejection, necessitated by the amendment of claim 24 in the reply filed 5/3/2010.

Regarding claims 24, 28 and 29, Garger et al teach a DNA molecule comprising cDNA of a tobacco mosaic virus (TMV) vector that contains a coding sequence of a protein fused to the native coat protein coding sequence, where the 3' end of the viral cDNA is immediately followed by a self-processing ribozyme sequence from satellite tobacco ringspot virus RNA (e.g., paragraphs [0002], [0008], [0010], [0050], [0059], [0068], [0077], [0100]-[0122]).

Regarding claim 31, Garger et al teach that the coding sequence of the protein is fused to the coat protein, which is preferably under the control of the coat protein promoter of the virus (e.g., paragraphs [0008], [0066] and [0100]-[0122]).

Regarding claim 37, the plasmid DNA taught by Garger et al (e.g., paragraphs [0100]-[0122]) would necessarily be capable of being incorporated into the genome of a plant cell by non-homologous recombination.

Regarding claim 39, a kit is a collection of items. Garger et al teach a DNA fragment of claim 24 and a vector comprising the DNA fragment of claim 24 (paragraphs [0002], [0008], [0010], [0050], [0059], [0068], [0077] and [0100]-[0122]).

Regarding claim 40, Garger et al teach an *E. coli* transformant comprising the vector comprising the DNA molecule (e.g., paragraphs [0100]-[0122] and [0143]-[0149], especially paragraph [0149]).

Response to Arguments - 35 USC § 102

The rejection of claims 24-29, 31, 32, 37, 39 and 40 under 35 U.S.C. 102(b) as being anticipated by Rasochova et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/3/2010. Rasochova et al do not teach that the ribozyme sequence includes a sequence of satellite tobacco ringspot virus.

The rejection of claims 24-26, 30, 31, 37, 39 and 40 under 35 U.S.C. 102(b) as being anticipated by Mori et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/3/2010. Mori et al do not teach that the virus vector originates in a plant virus that has a suppressor against a silencing reaction of plants.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garger et al (US Patent Application Publication No. 2002/0061309 A1; see the entire reference) in view of Zuo et al (US Patent No. 6,452,068 B1, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of independent claim 24 in the reply filed 5/3/2010.

The teachings of Garger et al are described above and applied as before. Further, Garger et al teach that the expression of the coat protein fusion proteins may be driven by any of a variety of promoters functional in the genome of the recombinant plant viral vector, where the protein is expressed by a promoter 5' to the fusion protein encoding region (e.g., paragraph [0066]). Moreover, Garger et al teach that the expression of the fusion protein may be elevated or controlled by a variety of plant or viral transcription factors (e.g., paragraph [0066]). Garger et al teach transcription of the viral mRNA including the coat protein fusion and 3' ribozyme sequence from a T7 promoter placed 5' to all of the sequences (e.g., paragraphs [0077], [0147] and [0149]).

Garger et al do not teach the DNA molecule where the viral mRNA including the coat protein fusion are transcribed under control of an inducible promoter that is located upstream of the virus vector cDNA and ribozyme sequence, where the inducible promoter is (i) 6XUASgal4 or (ii) O_{LexA}-46, and the DNA fragment further comprises a transcription factor for controlling transcription induced by the inducible promoter, where the transcription factor is (i) GVG or (ii) XVE.

Zuo et al teach a single vector comprising a promoter operably linked to a transcription factor and a promoter regulated by the transcription factor operably linked to a protein coding gene (e.g., column 9, line 27 to column 11, line 2). Zuo et al teach the vector where the transcription factor is a chimeric transcription factor in which the regulatory region of the rat glucocorticoid receptor (GR) is added to the DNA-binding domain of the yeast transcription factor GAL4 and the transactivating domain of the herpes viral protein VP16, where the chimeric transcription factor is called GVG (e.g., column 9, lines 50-67). When the vector comprises the GVG transcription factor, the inducible promoter contains six copies of the GAL4 upstream activating sequence (UAS) (6xUASGal4, e.g., column 9, lines 50-67; Figure 1). Zuo et al teach another construct referred to as XVE, which is similar to the GVG system but contains the DNA binding domain of the bacterial repressor LexA and the regulatory region of the human estrogen receptor (e.g., column 10, lines 43-53). Zuo et al specifically teach that the XVE construct can be used in place of the GVG construct as long as the proper inducer is used for the construct being used (e.g., column 10, lines 48-51). When the vector comprises the XVE transcription factor, the inducible promoter contains eight copies of LexA binding sites fused to the 35S minimal promoter at -46 (O_{LexA}-46; e.g., paragraph bridging columns 20-21; Figure 13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector of Garger et al et al to include the GVG coding sequence and the 6XUASgal4 promoter, because Zuo et al teach it is within the ordinary skill in the art to use a single vector for expression of a transcription factor for regulating an inducible promoter and for expression of a protein operably linked to the inducible promoter when the GVG transcription factor and 6XUASgal4 promoter is contained in the vector, and Garger et al teach the use of the vector for expression of a protein, where any promoter, such as a regulatable promoter, is used. With regard to claim 36, it would have been obvious to further modify the single vector comprising the GVG coding sequence and 6XUASgal4 sequence to replace the GVG coding sequence with the XVE coding sequence and to replace the 6XUASgal4 promoter with the O_{LexA}-46 promoter, because Zuo et al specifically teach that the XVE system can be used in place of the GVG system as long as the appropriate inducer is used.

One would have been motivated to make such a modification in order to receive the expected benefit of providing regulatable expression of the coat protein fusion as suggested by Garger et al with the regulatable system taught by Zuo et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 46-48, 50, 51 and 56-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of David et al (Plant Physiology, Vol. 125,

pages 1548-1553, April 2001, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

Mori et al teach a process for producing a transformant for protein production, comprising (i) transforming *N. benthamiana* host cells with a GVG transcription factor-expressing DNA fragment in which the GVG coding sequence is operably linked to the CaMV 35S promoter; where transforming is done by an Agrobacterium method (ii) screening the transformants obtained in step (i) for an individual F0 plant expressing GVG; and (iii) crossing the F0 GVG-expressing plants with 2FR plants containing cDNA of a virus vector that has been constructed by inserting a coding gene of human gamma interferon (IFN) into an RNA virus, where the IFN coding sequence is ligated to the 6XUASGal4 inducible promoter, which is induced by the GVG transcription factor (e.g., page 82, *Production of transgenic plants containing cDNA of RNA1 or cDNAs of both RNA2 and FCP2IFN*; pages 82-83, *Induced replication of FCP2IFN and subgenomic mRNA amplification in GVG1 x 2FR plants*; page 85, *Transformation of Nicotiana benthamiana*; Figure 1). Specifically, the virus vector used in the method of Mori et al contains a cDNA of a Brome mosaic virus that has been constructed by inserting a coding sequence of a human gamma interferon (IFN) protein into the RNA virus, and ligating a ribozyme sequence to the 3' end of the virus vector cDNA (e.g., page 85, paragraph bridging columns; Figure 1). The ribozyme sequence is a ribozyme sequence of satellite tobacco ringspot virus (e.g., page 85, paragraph bridging columns). In the virus vector, the IFN sequence was inserted in place of the coat protein gene (e.g., page 80, right column, 2nd full paragraph). Further, Mori et al teach a transformant produced by the abovementioned process, where the transformant produces IFN protein in the presence of dexamethasone (e.g., Figure 4). Mori et al

teach that the GVG transcription factor has a property of being activated by the hormone dexamethasone, a synthetic steroid hormone (e.g., page 82, *Analysis of the accumulation of RNA1 in response to DEX treatment*). Mori et al teach the method where the virus vector originates in a virus that is a Brome mosaic virus, which is a single strand (+) RNA plant virus (e.g., page 80, right column, 2nd full paragraph). With regard to claim 64, a kit is a collection of items, and Mori et al teach at least one item for use in the process of producing the abovementioned transformant (e.g., page 85, Experimental procedures).

Mori et al do not teach the method where the GVG transformants are further transformed with the cDNA of a virus vector that encodes IFN using an Agrobacterium method. Further, Mori et al do not teach the method where the cells are tobacco BY-2 cells.

David et al teach that the tobacco (*Nicotiana tabacum*) BY2 cell line is well characterized, highly homogenous, and shows an exceptionally high growth rate (e.g., page 1548, left column, 1st paragraph). Further, David et al teach that BY2 cells can be easily transformed without the need for protoplast preparation and stable transgenic calli, and suspension-cultured cells are easily obtained (e.g., page 1548, left column, 1st paragraph). David et al teach a method that brings together the advantages of the BY2 cell line with the advantages of the tetracycline derepressible system (e.g., page 1548, right column, full paragraph). David et al teach a method for producing a transformant for protein production, comprising (i) transforming BY2 cells with pBinTet1 vector, containing tetR under the control of the cauliflower mosaic virus (CaMV)-35S promoter; (ii) selecting clonal and stable transformants, named BY2-tetR, on kanamycin medium; (iii) and transforming the BY2-tetR cells with a pTX-Gus-int, a vector containing β-glucuronidase (Gus) under the control of the "Triple-Op"

promoter coupled with CaMV 35S (e.g., paragraph bridging pages 1548-1549; page 1549, left column). David et al teach that Gus activity was induced in the BY2-tetR cells comprising pTX-Gus-int by the addition of AhTc (e.g., Figure 1). David et al teach that a high steady-state expression of tetR ensures an efficient repression of the "Triple-Op" promoter (e.g., paragraph bridging pages 1549-1550). David et al teach Agrobacterium-mediated transformation of the BY2 cells (e.g., page 1552, Cell Transformation).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Mori et al to include a first Agrobacterium-mediated transformation step of BY2 cells with the GVG expression vector, and a second Agrobacterium-mediated transformation step of BY2 cells with the IFN expression vector, as taught by David et al because David et al teach it is within the ordinary skill in the art to use BY2 cells for regulated expression of a protein product and Mori et al teach regulated expression of the IFN protein product.

One would have been motivated to make such a modification in order to receive the expected benefit of selecting for BY2 GVG transformants with desirable levels of GVG expression prior to transformation with the IFN expression vector, because David et al teach that desirable levels of tetR could be identified prior to the second transformation step. It would have been within the ordinary skill of the art to transform the BY2 cells based upon the teachings of David et al, and it would have been within the skill of the art to screen for desirable levels of GVG by Northern blotting as taught by Mori et al. Furthermore, one would have been motivated to perform a second transformation step in BY2 cells rather than produce plants and cross the plants as taught by Mori et al in order to save time, because David et al teach that BY2 cells have

an exceptionally high growth rate and are easy to transform. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of David et al (Plant Physiology, Vol. 125, pages 1548-1553, April 2001, cited in a prior action; see the entire reference) as applied to claims 46-48, 50, 51 and 56-64 above, and further in view of Zuo et al (US Patent No. 6,452,068 B1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

The combined teachings of Mori et al and David et al are described above and applied as before.

Mori et al and David et al do not teach the method where the transcription factor is LexA-VP16-hER, the inducible promoter is O_{LexA}-46, and the inducer is estrogen.

Zuo et al teach the vector where the transcription factor is a chimeric transcription factor in which the regulatory region lf the rat GR is added to the DNA-binding domain of the yeast transcription factor GAL4 and the transactivating domain of the herpes viral protein VP16, where the chimeric transcription factor is called GVG (e.g., column 9, lines 50-67). When the vector comprises the GVG transcription factor, the inducible promoter contains six copies of the GAL4 upstream activating sequence (UAS) (6xUASGal4, e.g., column 9, lines 50-67; Figure 1).

Zuo et al teach another construct referred to as XVE, which is similar to the GVG system but contains the DNA binding domain of the bacterial repressor LexA and the regulatory region of the human estrogen receptor (e.g., column 10, lines 43-53). Zuo et al specifically teach that the XVE construct can be used in place of the GVG construct as long as the proper inducer is used for the construct being used (e.g., column 10, lines 48-51). When the vector comprises the XVE transcription factor, the inducible promoter contains eight copies of LexA binding sites fused to the 35S minimal promoter at -46 (O_{LexA}-46), and the inducer is estrogen (e.g., Example 12; Figure 13).

Mori et al and David et al both teach the use of regulatable transcription factors capable of being modulated for regulated expression of a protein. Mori et al specifically teaches the use of the GVG system, and Zuo et al specifically teaches that it was within the skill of the art to substitute the XVE system for the GVG system in order to achieve the predictable result of providing inducible expression of a protein. The XVE system comprises the claimed LexA-VP16-hER transcription factor, which is activated by estrogen, and the O_{LexA}-46 promoter.

Claims 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of David et al (Plant Physiology, Vol. 125, pages 1548-1553, April 2001, cited in a prior action; see the entire reference) as applied to claims 46-48, 50, 51 and 56-64 above, and further in view of Rasochova et al (US Patent Application Publication No. 2003/0074677 A1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 3/3/2010 and is reiterated below.

The combined teachings of Mori et al and David et al are described above and applied as before.

Mori et al and David et al do not teach the method where the virus vector comprises tobacco mosaic virus.

Rasochova et al teach a vector comprising cDNA of an RNA virus vector that has been constructed by inserting an exogenous RNA component and a ribozyme sequence at the 3' region (e.g., paragraph [0049]). Rasochova et al teach the vector where the exogenous RNA component has a coding function in which the RNA acts as a messenger RNA, encoding a sequence which, when translated by the host cell, results in the synthesis of a peptide or protein (e.g., paragraph [0047]). Rasochova et al teach the vector where the virus vector originates in a virus that is a single strand (+) RNA virus, such as tobacco mosaic virus (e.g., paragraphs [0042], [0135], [0139] and [0141]). Rasochova et al teach the DNA molecule where the exogenous RNA component is inserted in place of the coat protein coding sequence (e.g., paragraphs [0057] and [0137]). Rasochova et al teach the use of the vector to make transgenic plants expressing the protein (e.g., paragraphs [0138]-[0141]). Further, Rasochova et al teach it is within the skill of the art to use an inducible promoter for the expression of the exogenous RNA component (e.g., paragraphs [0049]-[0050]).

Because Mori et al and Rasochova et al both teach vectors for the expression of a protein in plant cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tobacco mosaic virus vector of Rasochova et al for the Brome mosaic virus vector of Mori et al, where expression of the protein is under the control of

the 6xUASgal4 promoter, in order to achieve the predictable result of providing a vector for the inducible expression of a protein in a plant cell.

Claims 32-34 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garger et al (US Patent Application Publication No. 2002/0061309 A1; see the entire reference) in view of Martinez et al (The Plant Journal, Vol. 19, No. 1, pages 97-106, 1999, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of independent claim 24 in the reply filed 5/3/2010.

The teachings of Garger et al are described above and applied as before. Further, Garger et al teach that the expression of the coat protein fusion proteins may be driven by any of a variety of promoters functional in the genome of the recombinant plant viral vector, where the protein is expressed by a promoter 5' to the fusion protein encoding region (e.g., paragraph [0066]). Moreover, Garger et al teach that the expression of the fusion protein may be elevated or controlled by a variety of plant or viral transcription factors (e.g., paragraph [0066]). Garger et al teach transcription of the viral mRNA including the coat protein fusion and 3' ribozyme sequence from a T7 promoter placed 5' to all of the sequences (e.g., paragraphs [0077], [0147] and [0149]).

Garger et al do not teach the DNA molecule where the viral mRNA including the coat protein fusion are transcribed under control of an inducible promoter that is located upstream of the virus vector cDNA and ribozyme sequence, where the inducible promoter is GRE, the transcription factor that controls transcription induced by the inducible promoter is a chimeric ecdysone receptor protein including a glucocorticoid receptor (GR) activation domain, a GR

DNA binding domain (DBD), a herpesvirus transactivation domain, and a *Heliothis virescens* ecdysone receptor (HecR) ligand binding domain (LBD).

Martinez et al teach a vector comprising an inducible GRE promoter upstream of a sequence to be transcribed and translated, and upstream of an expression cassette for the expression of a ligand-regulated transcription factor (e.g., Figure 1(b)). Martinez et al teach a vector encoding a transcription factor where the transcription factor is a chimeric protein comprising sequences of ecdysone receptors (EcR), glucocorticoid receptors (GR), and herpesvirus sequence (e.g., pages 97-98, Introduction; Figure 1). Martinez et al teach that HecR or HEcR refers to *Heliothis virescens* ecdysone receptor (e.g., paragraph bridging pages 97-98; page 98, paragraph bridging columns; page 99, right column, full paragraph; Figure 1(b)). Specifically, Martinez et al teach a vector encoding GR activation domain (GR Act), herpesvirus VP16 transactivation domain, GR DBD, and HecR LBD (e.g., Figure 1(b)). This vector encodes a chimeric protein of ecdysone receptors that comprises GR Act and DBD, herpesvirus transactivation domain, and HecR LBD. Martinez et al teach that the chimeric protein is inducible by the steroid hormone ecdysone or the ecdysone analog muristeroneA (e.g., paragraph bridging pages 97-98; page 100, left column, 1st full paragraph; page 103, left column, last full paragraph). Addition of muristeroneA to a plant transformed with the vector ES-60, which encodes the chimeric transcription factor, results in activation of expression from GRE also present in the vector, leading to detection of GUS protein (e.g., page 100, left column, 1st full paragraph; Figure 1(b)). Martinez et al teach that the inducible system is flexible, in that a strong activator (i.e., VP16) has been successfully used to enhance performance and is useful in both research and commercial applications (e.g., page 103, left column, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the DNA fragment of Garger et al to include a GRE promoter upstream of the RNA virus and 3' ribozyme sequence, as well as the expression cassette encoding the ecdysone-responsive transcription factor taught by Martinez et al because Garger et al teach it is within the ordinary skill in the art to regulate the expression of the coat protein fusion, and Martinez et al teach that the GRE and ecdysone-responsive transcription factor can be used for regulated expression.

One would have been motivated to make such a modification in order to receive the expected benefit of using a flexible system that acts as a strong activator of transcription as taught by Martinez et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 32-36 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of Zuo et al has been withdrawn in view of Applicant's amendment to independent claim 24 in the reply filed 5/3/2010.

The rejection of claim 55 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al is moot in view of Applicant's cancellation of the claim in the reply filed 5/3/2010.

With respect to the rejection of claims 46-48, 50, 51 and 56-64 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al, Applicant's arguments filed 5/3/2010 have been fully considered but they are not persuasive.

The response asserts that Mori et al teach inserting a RNA1-cDNA fragment into a binary transformation vector or plasmid instead of constructing cDNA of a virus vector by inserting a coding gene of an arbitrary protein into an RNA virus.

This argument is not found persuasive. While Mori et al do teach the insertion of the RNA1-cDNA fragment into a vector, Mori et al also teach constructing cDNA of a virus vector by inserting a coding gene of an arbitrary protein into an RNA virus. Specifically, Mori et al teach that the coding sequence of the IFN gene was inserted into the position normally occupied by the coat protein gene of brome mosaic virus (e.g., page 80, right column, 2nd full paragraph) and cDNA of the virus encoding the IFN protein was ligated to an inducible promoter (e.g., page 85, paragraph bridging columns). The teachings of Mori et al read on this aspect of the claimed invention, and Applicant has not distinguished this aspect of the claimed invention from the teachings of Mori et al.

The response notes that Mori et al cross a GVG-expressing plant with a 2FR-expressing plant, rather than use two transformation steps.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection of record is based upon the combined teachings of Mori et al and David et al. In the Office action mailed 3/3/2010,

the Examiner acknowledged that Mori et al do not teach the second transformation step (page 13). However, this deficiency is met by David et al.

The response notes that David transforms a plasmid at two different stages. However, the response asserts that the plasmids are different in terms of efficient expression, specifically the plasmid vector has a sufficiently high expression efficiency. The response asserts that one would not have been motivated to insert a virus vector at two different stages as is recited in independent claim 46, because the plasmid vector of David already achieves an enhanced expression efficiency.

These arguments are not found persuasive. First, it is noted that the claims do not require one "to insert a virus vector at two different stages" as asserted by the response. The claims require two transforming steps: (i) transforming a host cell with a DNA fragment comprising a coding sequence of a transcription factor ligated to a promoter for expressing the transcription factor; and (ii) transforming a host cell resulting from the first transformation step (which expresses the transcription factor) with a "DNA fragment in which cDNA of a virus vector that has been constructed by inserting a coding gene of an arbitrary protein into an RNA virus is ligated to an inducible promoter which is induced by the transcription factor." Thus, only the second transformation step is transformation of a "virus vector." Second, David et al teach that both transformation steps are required for inducible expression. David et al teach that high steady-state expression of tetR (from the first transformation) allows efficient expression from the "Triple-Op" promoter introduced in the second transformation (e.g., paragraph bridging pages 1548-1549; page 1549, left column; paragraph bridging pages 1549-1550). Thus, the assertion that "sufficiently high expression efficiency" is obtained with the first transformation

relates only to the expression of the transcription factor. Both the transcription factor and the second vector comprising the inducible promoter are required for inducible expression from the inducible promoter. Based upon the teachings of Mori et al and David et al, one would not stop after a single transformation or the introduction of a single plasmid encoding only the transcription factor. As stated in the rejection of record, one would have been motivated to make such a modification to receive the expected benefit of selecting for BY2 GVG transformants with desirable levels of GVG expression prior to transformation with the IFN expression vector, because David et al teach that desirable levels of tetR could be identified prior to the second transformation step (Office action mailed 3/3/2010, page 14). In other words, one selects the cells expressing the transcription factor at desirable levels prior to transformation with the IFN expression vector without having to make separate plants containing each of the vectors, thereby saving time and achieving a desirable result. David et al teach that BY2 cells have an exceptionally high growth rate and are easy to transform.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claim 49 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al, and further in view of Zuo et al, Applicant's arguments filed 5/3/2010 have been fully considered but they are not persuasive.

The response asserts that the Examiner has failed to show how David and Zuo remedy the deficiencies of Mori with respect to independent claim 24. The response asserts that claim 49 is dependent on claim 24.

This argument is not found persuasive. Claim 49 depends from claim 48, which depends from claim 47. Claim 47 depends from independent claim 46. Thus, claim 49 does not depend from claim 24. Accordingly, the limitations not taught by Mori with regard to claim 24 are those limitations not present in claim 49.

If Applicant intended to assert that Mori et al do not teach "a virus vector that has been constructed by inserting a coding gene of an arbitrary protein into an RNA virus is ligated to an inducible promoter which is induced by the transcription factor," these arguments are still not persuasive. Specifically, Mori et al teach that the coding sequence of the IFN gene was inserted into the position normally occupied by the coat protein gene of brome mosaic virus (e.g., page 80, right column, 2nd full paragraph) and cDNA of the virus encoding the IFN protein was ligated to an inducible promoter (e.g., page 85, paragraph bridging columns). The teachings of Mori et al read on this aspect of the claimed invention, and Applicant has not distinguished this aspect of the claimed invention from the teachings of Mori et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 52-54 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al, and further in view of Rasochova et al, Applicant's arguments filed 5/3/2010 have been fully considered but they are not persuasive.

The response asserts that the Examiner has failed to show ho David and Rasochova remedy the deficiencies of Mori with respect to independent claim 46.

This argument is not found persuasive, because the teachings of Rasochova et al are not relied upon for the rejection of claim 46. Claim 46 is properly rejected under 35 U.S.C. 103(a) for the reasons explained in prior actions and for the reasons set forth above.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

The rejection of claims 32-34 and 65 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of Martinez et al has been withdrawn in view of Applicant's amendment to independent claim 24 in the reply filed 5/3/2010.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636